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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/876,132	06/23/1997	TIMOTHY FOWLER	CG372	4697

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/876,132	FOWLER ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 23 June 1997. The preliminary amendments filed 27 August 1998 and 3 September 1999 have been entered. Claims 1-20 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-17, in Paper No. 17 (filed 24 June 2003) is acknowledged. Applicant first asserts that claim 6, directed to a method for preparing an improved *Enterobacteriaceae* strain wherein in a cryptic plasmid comprising SEQ ID NO: 1 or 2 is eliminated, is a linking claim which unites Inventions I-III. However, according to M.P.E.P. 809.03, a linking claim is a claim that is inseparable from two or more properly divisible inventions. Claim 6 does not link Group I to Groups II or III because Group I is directed to a different statutory class of Invention and is separable from the Inventions of Groups II and III for the reasons stated in the restriction requirement.

Next applicant argues that Inventions II and III are related to each other as portions of the nucleic acid sequence of pS. This argument is persuasive and restriction between groups II and III is withdrawn.

Applicant argues that, because the polypeptide of Invention IV is the deduced amino acid sequence encoded by SEQ ID NO: 3, "the deletion of the crytic [sic] plasmid that has the deduced amino acid sequence encoded by Invention IV is useful within the method of the present invention" (page 2). This argument is not found persuasive because, as pointed out in the previous Office Action, the polypeptide of Invention III is neither used in nor made by the

method of Invention I as claimed. Thus, the Groups are directed to different statutory classes of invention which are independent and distinct.

Finally, Applicant cites M.P.E.P. 803.04 and argues that Groups II-IV should be examined together because they encompass only 3 sequences. First, as the restriction requirement between Groups II and III has been withdrawn for the reasons provided above, the argument is moot with respect to rejoinder of the nucleic acid sequences. Next, the passage cited by applicant, pertains only to examination of multiple independent and distinct nucleic acid sequences in a single case. M.P.E.P. 803.04 provides no guidance as to examination of nucleic acids and proteins in a single application. For the reasons set forth in the previous Office Action, the protein of Invention IV is distinct from the nucleic acids of Inventions II and III. Furthermore, as each of the sequences requires a separate search, examining the protein with the nucleic acids places an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention.

Drawings

The drawings are objected to for the reasons indicated on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims of the instant invention are directed to a method for preparing an improved *Enterobacteriaceae* strain or reducing the mobilization properties of plasmids residing within an *Enterobacteriaceae* strain comprising eliminating a cryptic plasmid from a progenitor strain. Claims are also directed to bacteria made by the method.

The Written Description Guidelines state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 1, page 1105). In the instant case, as the progenitor strain is the starting material used in the method, said progenitor strain is a critical element of both the method and the products of the method and must be adequately described.

The specification defines a "progenitor strain" as an *Enterobacteriaceae* strain containing a cryptic plasmid (page 4, lines 3-4) and a "cryptic plasmid" as a plasmid found naturally in an *Enterobacteriaceae* strain which when deleted from the progenitor strain alters the phenotypic

growth characteristics or alters mobilization properties of other *Enterobacteriaceae* resident plasmids. Furthermore, the specification defines "improved" as having at least one desirable phenotypic modification of the progenitor strain (page 4, lines 25-29). Thus, the progenitor strain of the instant application is generic to any *Enterobacteriaceae* strain comprising a plasmid which alters the growth or mobilization characteristics of said *Enterobacteriaceae* such that when the plasmid is eliminated the growth characteristics are improved or the mobilization properties are reduced.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" and "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406" MPEP §2163(3)(a)(ii). (Federal Register, Vol. 66, No. 4, Column 3, page 1106).

With regard to reduction to practice, the instant disclosure provides a single example of a progenitor strain useful in the instant claimed method (i.e., *Pantoea citrea* comprising the 3.8 Kb pS plasmid; see especially Example II). Clearly, however, this single example is not representative of the genus of any *Enterobacteriaceae* strain comprising a plasmid which alters the growth or mobilization characteristics of said *Enterobacteriaceae* such that when the plasmid

is eliminated the growth characteristics are improved or the mobilization properties are reduced. Thus, it is incumbent upon Applicant to disclose the relevant, identifying characteristics of the progenitor strain sufficient to demonstrate possession of the claimed genus. It should be noted that the art teaches that inhibition of growth and increased mobilization characteristics are not universal phenotypic markers for the presence of naturally occurring bacterial plasmids. In a survey of phenotypes associated with large plasmids, Hardman *et al.* (1985) *Microbiol. Sci.* 2:90-94 fails to mention growth inhibition or increased mobilization characteristics (see especially Table 1), suggesting that such phenotypes are not prominently associated with large plasmids. Furthermore, on page 2, paragraph 2, the specification characterizes the improved growth characteristics obtained upon elimination of the cryptic plasmid from *E. pantoea* as "unexpected". Likewise, on page 2, paragraph 3, the specification characterizes the reduced mobilization obtained upon elimination of pS from *E. pantoea* as "unexpected". These teachings clearly indicate that improved growth characteristics and reduced mobilization properties are not obtained upon elimination of all plasmids from bacteria and the teachings from the specification indicate that this phenotype is actually uncommon enough that the phenotypes are not expected when plasmids are eliminated. Thus, the phenotypic characteristics to which the claims are limited will be obtained only upon the elimination of some subset of naturally occurring bacterial plasmids.

Although the cryptic plasmid of the claims is limited by the definition set forth in the specification to only those plasmids which when deleted from the progenitor strain alters the phenotypic growth characteristics or alters mobilization properties of other *Enterobacteriaceae* resident plasmids, the specification sets forth no structural limitations which are correlated with

these functional limitations aside from the pS plasmid comprising both SEQ ID NO: 1 and SEQ ID NO: 2. An adequate written description of a plasmid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the plasmid itself. It is not sufficient to define plasmid solely by its principal biological property (i.e., when deleted it alters the phenotypic growth characteristics or alters mobilization properties of other *Enterobacteriaceae* resident plasmids), because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any plasmid, or progenitor strain comprising said plasmid, with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method that requires possession of all progenitor *Enterobacteriaceae* strains that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any *Enterobacteriaceae* strain comprising a plasmid which alters the growth or mobilization characteristics of said *Enterobacteriaceae* such that when the plasmid is eliminated the growth characteristics are improved or the mobilization properties are reduced. Therefore, only the described *Pantoea citrea* strain comprising the cryptic plasmid pS, which comprises

both SEQ ID NO: 1 and SEQ ID NO: 2 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-5, 7-13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing an improved *Enterobacteriaceae* strain from a progenitor *Enterobacteriaceae* strain, wherein said progenitor *Enterobacteriaceae* strain comprises the cryptic plasmid pS, or an *Enterobacteriaceae* strain made by the method, does not reasonably provide enablement for the method or strain wherein the progenitor *Enterobacteriaceae* comprises a cryptic plasmid other than pS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: As described above, the claims are directed to a method for preparing an improved *Enterobacteriaceae* strain or reducing the mobilization properties of plasmids residing within an *Enterobacteriaceae* strain comprising eliminating a cryptic plasmid from a progenitor strain and to bacteria made by the method. Thus, thus the claims are directed to a method of using a progenitor *Enterobacteriaceae* strain comprising a cryptic plasmid, which is defined as a plasmid found naturally in an *Enterobacteriaceae* strain which when deleted from the progenitor strain alters the phenotypic growth characteristics or alters mobilization properties of other *Enterobacteriaceae* resident plasmids

State of the prior art and level of predictability in the art: As describe above, the art does not teach that the properties of the instant cryptic plasmid are universal to naturally occurring bacterial plasmids and does not provide a means to distinguish the instant cryptic plasmid from other naturally occurring plasmids. Thus, the teachings from the art do not provide means to identify a progenitor strain that could be used in the instant claimed method without resorting to blind trial and error experimentation to test each and every strain. Hardman *et al.* (*supra)* also teach that, at least with regard to large plasmids, assigning phenotypes to any given plasmid is problematical. Hardman *et al.* teaches, "[c]uring bacteria of large plasmids and associating loss of function with loss of plasmid is not always possible" (page 91, column 1, third full paragraph). Therefore, the art teaches that the phenotype obtained by eliminating any given plasmid is unpredictable and in some cases requires substantial experimentation to establish.

Amount of direction provided by the inventor and existence of working examples: As described above, the instant specification provides a single example of an *Enterobacteriaceae*

strain useful in the claimed method (i.e., *Pantoea citrea* comprising the 3.8 Kb pS plasmid), and teaches that the phenotype obtained upon elimination of the pS plasmid was unexpected. The disclosure is silent with regard to how to obtain other progenitor strains that could be used in the claimed method other than random trial and error experimentation.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to use the full scope of the claimed method or make the full scope of the claimed product without engaging in undue experimentation to isolate progenitor strains that could be used in the method. Given the unpredictability of phenotype obtained by eliminating any given plasmid from an *Enterobacteriaceae* strain and the absence of guidance in the art and instant disclosure that would enable the skilled artisan to identify strains useful in the claimed method, the skilled artisan would have to engage in blind trial and error experimentation to test each strain of *Enterobacteriaceae* comprising a unique plasmid to identify those strains useful in the method. As many plasmids are known to exist (see for example the Lederberg collection of approximately 1,000 naturally occurring bacterial plasmids at http://www.bayoubiolabs.com/lederber.htm) in bacteria and many more are likely to be discovered, the amount of experimentation required to make and use the full scope of the claimed invention would clearly be undue. Therefore, only the method wherein the progenitor strain is an *Enterobacteriaceae* strain containing the cryptic plasmid pS and an improved *Enterobacteriaceae* made by the method are enabled by the disclosure.

Claims 7 and 15 are additionally rejected under 35 U.S.C. 112, first paragraph, because the claims refers to biological deposits to satisfy the enablement requirement, but the disclosure does not indicate that a biological deposit was made according to the rules set forth for deposit of biological material (M.P.E.P. 2401-2411). The claims are drawn to a method of using a bacterial strain identified as ATCC accession number 31940. Because the complexity of a cell precludes independent derivation of another bacterial strain with substantially identical characteristics, one would have to have access to the ATCC in order to use the claimed invention. Without such availability practicing the invention is impossible and the claims are therefore not enabled. If the deposits are made under the terms of the Budapest Treaty, an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines or cells have been deposited under the Budapest treaty and that the cell line or cells will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. § 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

d) a test of the viability of the biological material was performed at the time of deposit (see 37 C.F.R. § 1.807); and,

e) the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Sykora *et al.* (1989) *Plasmid* 21:85-98 or Yoshikawa *et al.* (1967) *J. Bacteriol.* 93:245-253.

Both Sykora *et al.* and Yoshikawa *et al.* teach a method for preparing an improved *Enterobacteriaceae* strain (i.e., *E. coli*) from a progenitor strain comprising a cryptic plasmid, as it is defined in the first full paragraph on page 4 of the instant specification, said method comprising the step of eliminating the cryptic plasmid from the progenitor strain. In the right column on page 86, Sykora *et al.* teaches a method of curing a cryptic plasmid from F'lac bearing *E. coli.* Sykora *et al.* further teaches that the plasmid free cells have a higher per capita growth rate than plasmid containing cells (see especially lines 7 and 8 in Table 1 and the discussion in the first full paragraph in the left column on page 96). Thus, Sykora *et al.* teaches a

method of preparing an improved *Enterobacteriaceae* strain according to the instant claim 1 and a product *Enterobacteriaceae* according to the instant claim 16.

Yoshikawa *et al.* also teaches a method of curing a cryptic plasmid from R factor bearing *E. coli* using acradine orange and UV light and produce the plasmid free strain YC-74 from the plasmid bearing strain YC-73 (see especially the fourth paragraph on page 246 and Table 1). Yoshikawa *et al.* further teaches that the plasmid free cells have a higher growth rate than plasmid containing cells (see especially Table 4; compare YC-73 to YC-74). Thus, Yoshikawa *et al.* teaches a method of preparing an improved *Enterobacteriaceae* strain according to the instant claim 1 and a product *Enterobacteriaceae* according to the instant claim 16.

As Sykora *et al.* and Yoshikawa *et al.* teach a method of preparing an improved *Enterobacteriaceae* strain which comprises the same method steps as the instant method, and a product of that method, the teachings anticipate the instant claim 1 and 16.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

JAMES KETTER
PRIMARY EXAMINER